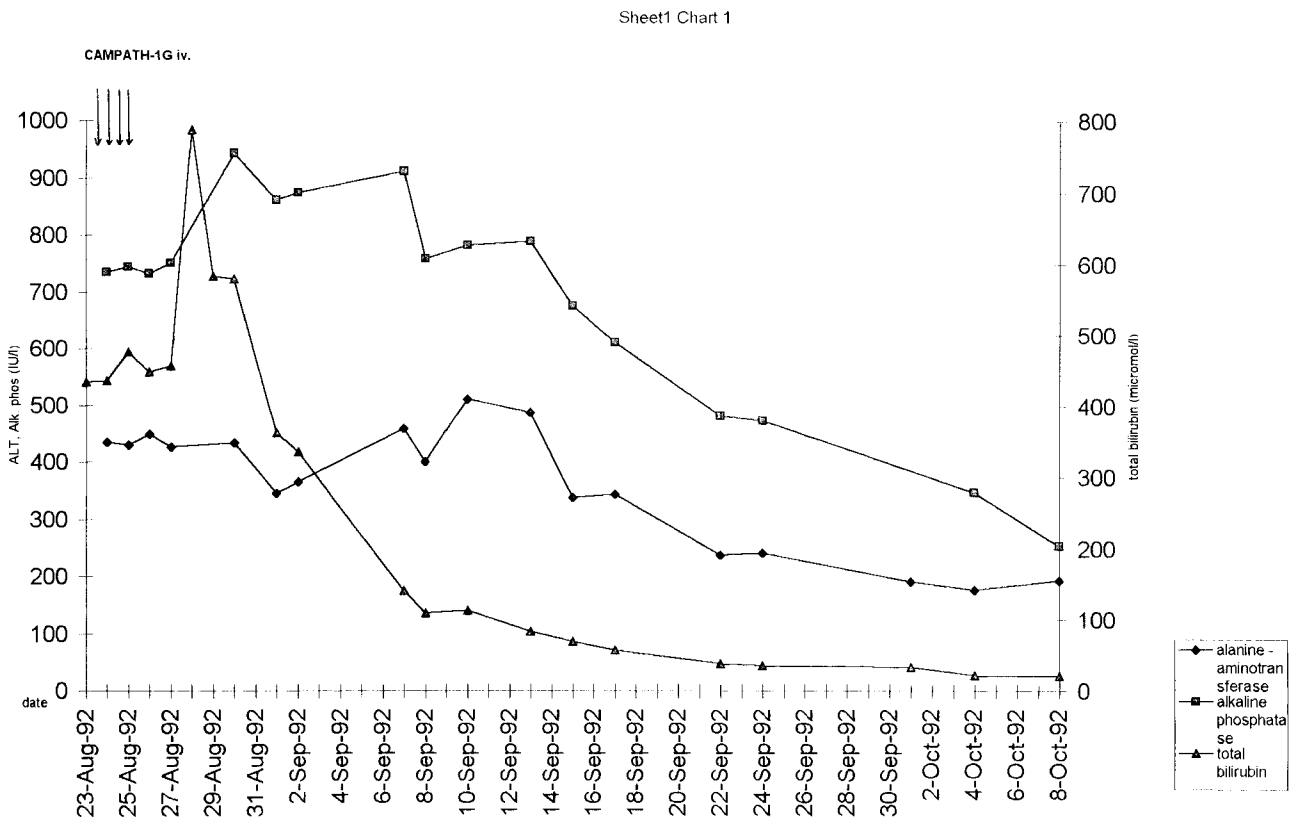

Fig. 1. Response to CAMPATH-1. Drastic improvement of liver function tests following CAMPATH-1 administration.

improved slowly, as well and this therapy was continued. The patient was discharged 1 month later with grade II GVHD, normal bilirubin, ALT 194 U/L, AST 116 U/L, ALP 204 U/L, and GGTP 891 U/L. Gradual and very slow improvement has continued.

Currently, 4 years after BMT, the patient is in hematologic and cytogenetic remission, (including polymerase chain reaction (PCR) negativity) with mild chronic GVHD, localized in the skin and liver.

During the past few years, CAMPATH-1 has been used successfully for the removal of immunocompetent T cells and natural killer (NK) cells, for the prevention of GVHD; in vivo CAMPATH-1 has also been used as an additional immunosuppressive agent in BMT preconditioning [2], and to treat autoimmune disorders, including rheumathoid arthritis [3]. Because of its anti-T and anti-NK activity, we concluded that CAMPATH-1 would also be a good candidate for the treatment of GVHD. In the case presented, CAMPATH-1 administration resulted in significant improvement of grade IV GVHD, manifesting mainly liver involvement. T cells have been previously shown to be involved in various liver pathogenesis and to be able to mediate severe liver damage. Moreover, we and others have demonstrated the ability of CAMPATH-1 to improve hepatitis and liver damage associated with severe aplastic anemia [5].

In light of this case, we suggest including CAMPATH-1G therapy for severe, life-threatening aGVHD when other therapeutic modalities have failed. The next step is to elucidate the role of CAMPATH-1 in anti-GVHD therapy and comfirming these findings on a large group of patients.

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Congenital Afibrinogenemia: Treatment of Excessive Menstrual Bleeding With Continuous Oral Contraceptive

To the Editor: We read with interest the correspondence of Castman et al. [1] about inhibition of ovulation by oral contraceptive in patients with congenital afibrinogenemia, in order to prevent hemoperitoneum. We report our recent experience with such treatment for excessive menstrual bleeding.

Our patient, a 13-year-old girl, was found to have congenital afibrinogenemia in the neonatal period following bleeding from the umbilical cord stump. She was treated with repeated fibrinogen concentrate infusion. Coagulation studies at that time showed unmeasurable immunoreactive fibrinogen and bleeding time >30 min. Platelet count, platelet aggregation in response to adenosine diphosphate, and activity of FVIII/von Willebrand factor (vWF) were normal. Inheritance of the defect appeared to be autosomal recessive, as both parents were first cousins, had mildly reduced fibrinogen concentration and were asymptomatic [2]. Neither her three sisters nor two brothers were affected. She was referred to the gynecology clinic because of prolonged and excessive menstrual bleeding since menarche, 3 months previously, not responding to treatment with fibrinogen concentrate infusion (12 g over 3 months). Hemoglobin was 8.2 g/dl. Oral contraceptive (0.03 mg ethinylestradiol and 150 mg levonorgestrel) was prescribed without a break in pill taking, in order to inhibit subsequent menstruation. Bleeding stopped 2 days later without further menstrual periods over a 3-month follow-up. Hemoglobin is now 9.4 g/dl.

The use of oral contraceptive to inhibit ovulation in women with congenital afibrinoginemia was described by Bottini et al. [3] as a phrophylactic measure against hemoperitoneum caused by spontaneous rupture of corpus luteum. This complication is common, may recur, and does not always resolve with fibrinogen infusion, which leaves resection of ruptured ovarian tissue as only measure to control bleeding [1,3]. Besides the inherent risks of frequent use of blood products and of performing laparotomy in a patient with a bleeding disorder, removal of functioning ovarian tissues in young women has serious implications on future reproductive performance. We therefore agree that treatment with oral contraceptive is justified in women with congenital afibrinogenemia [1,3]. Although the first few ovarian cycles after menarche may be anovulatory without corpus luteum formation or risk of hemoperitoneum, as probably happened here, we recommend starting treatment as soon as possible after menarche because it is difficult to predict the onset of ovulation. Afibrinogenic women may sometimes have normal menstruation [4]. In such cases, oral contraceptive can be given for 21 days followed by a 7-day break, as usual, in order to inhibit ovulation and prevent hemoperitoneum. In patients with excessive menstrual bleeding, similar to our patient, the oral contraceptive should ideally be prescribed continuously without a break, in order to prevent menstruation as well as ovulation. Although oral contraceptive-withdrawal bleeding is usually of moderate amount, it is preferable not to expose those patients to any bleeding at all. The duration of contraceptive treatment in young women will depend on their reproductive wishes because these women can conceive [2]. Despite the finding that almost 90% of pregnancies reported were complicated by recurrent first trimester abortion, placental abruption and postpartum hemorrhage, successful outcome has been described in two women treated with fibrinogen replacement throughout pregnancy [5].

We therefore, believe, that oral contraceptive treatment is better given continuously to induce amenorrhea in women with congenital afibrinogenemia presenting with excessive menstrual blood loss.

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Hepatitis C Virus Infection in Waldenström's Macroglobulinemia

To the Editor: Recent reports suggest that some cases of Waldenström's macroglobulinemia (WM) are caused by hepatitis C virus (HCV) infection [1]. Previous studies from the Italian group suggested that HCV infection might also produce monoclonal gammopathies complicated by cryoglobulinemia (CG) [2]. We recently studied a case of WM following hepatocellular carcinoma in the course of chronic liver disease, suggesting that the persistent HCV infection and the history of alcohol abuse were involved in the pathogenesis of WM in this case (unpublished observation). Our preliminary report suggests the high incidence of HCV infection in B-cell malignancies in Japan [3].

We investigated four cases of WM since November 1992, when the assay system of HCV (enzyme immunoassay; EIA) was available at our institute. These four cases were all heterosexual Japanese. All the present cases of WM fulfilled the eligible criteria by Kyle and Garton [4]. Hepatitis B surface antigen (HBsAg) and antibody against HBsAg (HBsAb) were determined by EIA. Antibodies for HCV (HCVAb) were all examined by second generation EIA (Ortho Diagnostics Co., Raritan, New Jersey). We examined HCV-RNA in all the cases by reverse transcription-polymerase chain reaction (RT-PCR) assay, as described previously [5].

Table I shows the clinical characteristics of four cases. HCV-RNA was detected in only one of the four patients examined. The genotype of HCV was III (Okamoto's classification) in one case surveyed. CG was not present in any of the cases.

The incidence of HCV infection associated with WM is not well known. In our study, HCV infection was detected in only one of four WM patients examined. Santini et al. [1] reported that HCV-RNA was detected in all the examined cases. Nevertheless, three of our four WM cases were HCV-RNA negative. This finding is similar to the recent report by Mussini et al. [2]. However, RT-PCR was not done for the detection of HCV in this report. Although WM is usually diagnosed by an IgM value of >30 g/L, previous reports did not show the eligible criteria of WM. Therefore, secondary macroglobulinemia (<30 g/L of M component), such as type II mixed CG, might have been included in the previous studies. Since WM occurs in only 17% of patients with IgM monoclonal gammopathy [4], diagnosis based on the eligible criteria may be important.

A high incidence of B-cell malignancies is reported in HCV carriers associated with CG [2,6], suggesting that CG plays an important role in the pathogenesis of B-cell malignancies. In our patients, the onset of WM might be related to causes other than coexistence of CG, since CG was not documented. Type II mixed CG is endemic to the Mediterranean area, but, does not seem to be endemic in Japan. These findings suggest the heterogeneity in the pathogenesis of WM. Further studies are needed to clarify the involvement of HCV infection in the pathogenesis of WM.

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